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Articles

Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial

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Summary

Background **Emerging evidence suggests that stem cells and progenitor cells derived from bone marrow can be used to improve cardiac function in patients after acute myocardial infarction. In this randomised trial, we aimed to assess whether intracoronary transfer of autologous bone-marrow cells could improve global left-ventricular ejection fraction (LVEF) at 6 months' follow-up.**

Methods **After successful percutaneous coronary intervention (PCI) for acute ST-segment elevation myocardial infarction, 60 patients were randomly assigned to either a control group (n=30) that received optimum postinfarction medical treatment, or a bone-marrow-cell group (n=30) that received optimum medical treatment and intracoronary transfer of autologous bone-marrow cells 4·8 days (SD 1·3) after PCI. Primary endpoint was global left-ventricular ejection fraction (LVEF) change from baseline to 6 months' follow-up, as determined by cardiac MRI. Image analyses were done by two investigators blinded for treatment assignment. Analysis was per protocol.**

Findings **Global LVEF at baseline (determined 3·5 days [SD 1·5] after PCI) was 51·3 (9·3%) in controls and 50·0 (10·0%) in the bone-marrow cell group (p=0·59). After 6 months, mean global LVEF had increased by 0·7 percentage points in the control group and 6·7 percentage points in the bone-marrow-cell group (p=0·0026). Transfer of bone-marrow cells enhanced left-ventricular systolic function primarily in myocardial segments adjacent to the infarcted area. Cell transfer did not increase the risk of adverse clinical events, in-stent restenosis, or proarrhythmic effects.**

Interpretation **Intracoronary transfer of autologous bone-marrow-cells promotes improvement of left-ventricular systolic function in patients after acute myocardial infarction.**

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Introduction

Rapid reperfusion of the infarct-related coronary artery is of great importance in salvaging ischaemic myocardium and limiting the infarct size in patients with acute myocardial infarction. When done expeditiously and expertly, percutaneous transluminal coronary angioplasty with stent implantation is the method of choice to re-establish coronary flow.[1] Unfortunately, myocardial necrosis starts rapidly after coronary occlusion, usually before reperfusion can be achieved.[2] The loss of viable myocardium initiates a process of adverse left-ventricular remodelling, leading to chamber dilatation and contractile dysfunction in many patients.[3] In this context, much interest has followed from experimental studies showing that cardiac transfer of unfractionated bone-marrow cells, or stem cells and progenitor cells derived from bone marrow can enhance functional recovery after acute myocardial infarction.[4,5] Based on these data, stem cells and progenitor cells derived from bone marrow have been proposed for use in the repair of cardiac tissue after acute myocardial infarction in patients.[6-8]

Early clinical investigations indicate that infusion of autologous bone-marrow cells into the infarct-related coronary artery is feasible after acute myocardial infarction.[9,10] However, because these studies were not randomised trials, the efficacy of intracoronary transfer of bone-marrow cells for functional recovery after acute myocardial infarction in patients has remained uncertain. We did a randomised controlled trial to assess the effect of intracoronary transfer of autologous bone-marrow cells on left-ventricular functional recovery in patients after acute myocardial infarction and successful percutaneous coronary intervention (PCI).

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Methods

Patients

Patients were eligible if they were admitted within 5 days of the onset of symptoms of a first ST-segment elevation myocardial infarction, had undergone successful PCI with stent implantation in the infarct-related artery, and had hypokinesia or akinesia involving more than two thirds of the left-ventricular anteroseptal, lateral, and/or inferior wall, as shown by angiography done immediately after PCI. We excluded patients who had multivessel coronary artery disease, pulmonary oedema, cardiogenic shock, advanced renal or hepatic dysfunction, or documented terminal illness or cancer.

This randomised-controlled study of BOne marrOw transfer to enhance ST-elevation infarct regeneration (the BOOST trial) was approved by our local Ethics Committee. Patients provided written informed consent.

Randomisation and baseline cardiac MRI

Patients were randomly allocated in a 1:1 ratio to either the control or bone-marrow-cell groups, with use of sequentially numbered, sealed envelopes provided by IST (DM). After randomisation, all patients underwent cardiac MRI.

Harvest and transfer of bone-marrow cells

After baseline cardiac MRI, bone marrow was harvested from patients in the bone-marrow-cell group. Bone marrow was processed by 4% gelatine-polysuccinate density gradient sedimentation according to current Good Manufacturing Practice (GMP) regulations (Cytonet, Hannover, Germany), to reduce the volume of the preparation and to deplete erythrocytes and platelets. The final suspension of bone-marrow cells was washed and resuspended in saline with 10 000 U/L heparin.

We used an automated haemocytometer to measure the number of nucleated cells, packed-cell volume, and platelet count in the initial bone marrow aspirate and in the final preparation of bone-marrow cells. Nucleated cell viability was assessed by trypan blue exclusion. We measured the number of CD34+ cells with flow cytometry analysis (FACSCalibur, BD Biosciences, Heidelberg, Germany) using an antibody from Beckman Coulter (Krefeld, Germany). Haemopoietic colony-forming cell growth was measured by a methylcellulose assay (StemCell Technologies, St Katharinen, Germany).

6-8 h after bone-marrow harvest, the final preparation of bone-marrow cells was infused into the infarct-related artery via the central lumen of an over-the-wire balloon catheter (Concerto, Occam International, Eindhoven, Netherlands). To allow bone-marrow cells maximum contact time with the microcirculation of the infarct-related artery, the balloon was inflated inside the stent to transiently interrupt antegrade blood flow during infusions. The entire bone-marrow-cell preparation was infused during four to five coronary occlusions, each lasting 2·5-4 min. Between occlusions, the coronary artery was reperfused for 3 min.

Follow-up

All patients were treated with aspirin (300 mg daily for 4 weeks after PCI, then 100 mg daily), clopidogrel (300 mg loading dose, then 75 mg daily for at least 4 weeks after PCI), an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker, a ßblocker, and a statin (if LDL

cholesterol concentrations were above 2·6 mmol/L), unless these agents were contraindicated. At both 6 weeks and 3 months after discharge, patients had follow-up examinations to assess their clinical status and to review their current medication. Where necessary, dosages of angiotensin-converting enzyme inhibitors (ACE-inhibitors), angiotensin-receptor blockers, ßblockers, and statins were adjusted in accordance with current practice guidelines.[11,12] 6 months after discharge, cardiac MRI was repeated in all patients. In addition, patients were scheduled to undergo coronary angiography to assess the degree of restenosis in the stented segment of the infarct-related artery. Restenosis was quantified with a computer-based system (CMS, Medical Imaging Systems, Leiden, Netherlands) by an investigator unaware of treatment assignment (AM).

To assess whether intracoronary bone-marrow-cell transfer was associated with proarrhythmic effects, we obtained 24 h Holter recordings from all patients before hospital discharge, and at 6 weeks', 3 months', and 6 months' follow-up. From these recordings, the mean number of premature ventricular complexes per h was calculated. We also recorded the number of non-sustained and sustained ventricular tachycardias per recording. In addition, patients were scheduled to undergo programmed ventricular stimulation at 6 months' follow-up. Ventricular stimulation was done at the right-ventricular apex and the right-ventricular outflow tract with single, double, and triple extra stimuli at twice the diastolic threshold and basic cycle lengths of 500 ms and 400 ms.

Cardiac MRI

Cardiac MRI was done with the patient in supine position in a 1.5-T scanner (CV/i, General Electric, Munich, Germany) using electrocardiogram (ECG) gating and a four-element phased array receiver coil. To measure left-ventricular volumes, we used repeated breath-hold fast gradient echo sequences in a steady state (FIESTA, General Electric). Sequence parameters were as follows: TR/TE 3·8/1·6 ms, 40° flip angle, 224x224 matrix, field of view 36-38 cm, in-plane resolution 1·6x1·6-1·7x1·7 mm, 38-40 phases per RR-interval, 10 mm slice thickness. An end-diastolic, horizontal long-axis plane of the left ventricle at end-expiration provided the reference image on which a stack of contiguous short-axis slices was positioned to cover the entire left ventricle.

Contrast-enhanced MRI was used to assess myocardial injury after acute myocardial infarction.[13] A breath-hold k-space segmented T1 weighted inversion recovery gradient echo sequence was used to cover the entire left ventricle with 7-8 mm short-axis slices as described above (TR/TE 7·1/3·1 ms, 256x192 matrix, field of view 36-38 cm, in-plane resolution 1·4x1·9-1·5x2·0 mm). Inversion time (200-220 ms) was individually adapted to null the signal of the myocardium. End-diastolic images were obtained starting 15 min after an intravenous bolus injection of 0·15 mmol/kg gadobutrol, a gadolinium-based extracellular contrast agent (Schering, Berlin, Germany).

All image analyses were done by two investigators who were unaware of treatment assignment (CB and SF), using the MASS 4.0.1 software (Medical Imaging Systems). Endocardial and epicardial borders were traced in all end-diastolic and end-systolic short-axis slices to determine left-ventricular end-diastolic volumes (LVEDV) and end-systolic volumes (LVESV) for global and regional calculation of left-ventricular ejection fraction (LVEF), and left-ventricular mass. For assessment of infarct volumes, late contrast enhancement was quantified. LVEDV index, LVESV index, and left-ventricular-mass index were calculated by dividing LVEDV, LVESV, and left-ventricular mass by body surface area. Regional LVEF was derived by calculating LVEF only in slices showing late contrast enhancement at

baseline. Regional left-ventricular function was assessed by determining systolic wall motion in the infarct region and border zone. Systolic-wall motion was defined as the radial displacement of the endocardial contour at systole. Myocardial segments showing late contrast enhancement at baseline were defined as the infarct region. Segments adjacent to the infarct region were defined as the border zone.

Statistical analysis

Primary endpoint was the change from baseline in global LVEF at 6 months' follow-up. Secondary endpoints were changes in LVEDV index, LVESV index, left-ventricular-mass index, and late contrast enhancement. We calculated that we would need 30 patients in each group to achieve a power of at least 80% to detect a difference in global LVEF change of 5 percentage points between study groups, with a two-sided significance level of $p<0·05$, and a common standard deviation of 6·5 percentage points for the global LVEF change from baseline to 6 months' follow-up. We used ANCOVA to compare global LVEF changes in the two study groups, with bone-marrow-cell treatment as the main factor and LVEF at baseline as a covariate. To estimate the treatment effect, differences in least-squares means and corresponding 95% CI were calculated based on the ANCOVA model. We analysed secondary endpoints using the same methods. The consistency of the treatment effect on global LVEF change was assessed across several subgroups. All statistical tests were two-sided with a significance level of $p<0·05$.

Homogeneity of treatment groups at baseline was assessed using Student's *t* test for continuous variables showing no marked deviations from the normal distribution. For other continuous variables or ordinal baseline data, the Wilcoxon rank-sum test was used. Categorical baseline data were investigated using χ^2 tests. The relation between the number of nucleated cells, CD34+ cells, and haemopoietic colony-forming cells infused into the infarct-related coronary artery and subsequent global LVEF changes were assessed with Pearson's correlation coefficient. Subgroup analyses were not prespecified but were exploratory in nature. All subgroup analyses are reported.

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Results

Between January, 2002, and May, 2003, 78 patients were informed about the trial. 65 patients were randomly allocated to treatment. After randomisation, five patients were withdrawn because they could not undergo cardiac MRI, either because of claustrophobia or severe obesity. The final cohort included 30 controls and 30 patients in the bone-marrow-cell group (figure 1). Table 1 shows patients' baseline characteristics. All patients received optimum postinfarction medical treatment (table 1).

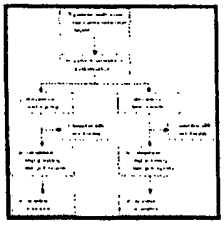

Figure1: **Trial profile**

BMC=bone-marrow cell.

	Control group (n=30)	BMC group (n=30)	p
Age (years)	59·2 (13·5)	53·4 (14·8)	0·11
Men	22 (73%)	20 (67%)	0·57
Body-mass index (kg/m^2)	26·2 (4·2)	25·8 (3·0)	0·67
Diabetes mellitus	3 (10%)	3 (10%)	1·0
Hyperlipidaemia*	7	9	0·56
Hypertension	13 (43%)	9 (30%)	0·28
Current cigarette use (number of patients)	17 (57%)	18 (60%)	0·79
Median time from symptom onset to PCI (h) (range)	8·0 (3-120)	9·8 (2-22)	0·92
Killip class			
1	25 (83%)	23 (77%)	0·51
2	5 (17%)	7 (23%)	
3 or 4	0	0	
Infarct-related artery			
Right coronary artery	7 (23%)	7 (23%)	1·0
Left coronary artery	23 (77%)	23 (77%)	
TIMI flow grade			
before PCI:			0·73
Grade 0 or I	16 (53%)	13 (43%)	
Grade II	13 (43%)	16 (53%)	
Grade III	1 (3%)	1 (3%)	
after PCI:			0·75
Grade 0 or I	0	0	
Grade II	7 (23%)	6 (20%)	
Grade III	23 (77%)	24 (80%)	
Maximum serum creatine kinase concentration (U/L)	2844 (1161)	2968 (1867)	0·77
Maximum serum creatine kinase MB concentration (U/L)	156 (51)	175 (123)	0·46
Maximum serum troponin T concentration (µg/L)	7·4 (4·4)	7·4 (5·5)	0·99
Periprocedural therapy			
Thrombolytic therapy before PCI	10 (33%)	14 (47%)	0·29
Platelet glycoprotein IIb/IIIa inhibitors		14 (47%)	14 (47%)
	1·0		
Median number of stents (range)	1 (1-5)	1 (1-2)	0·40
Size of stent (mm)	3·3 (0·4)	3·3 (0·4)	1·0
Length of stent (mm)	17·5 (9·6)	17·6 (6·4)	0·97
Lesion characteristics			0·71
Type A	8 (27%)	6 (20%)	
Type B	16 (53%)	19 (64%)	
Type C	6 (20%)	5 (3%)	
Medication at primary discharge:			
Aspirin† and clopidogrel	29 (97%)	30 (100%)	
ACE-inhibitors or angiotensin-	30 (100%)	30 (100%)	

receptor blockers		
ß blockers	30 (100%)	29 (97%)
Statins	29 (97%)	30 (100%)
at 6 months' follow-up:		
Aspirin†	27 (97%)	29 (97%)
ACE-inhibitors or angiotensin-receptor blockers	30 (100%)	30 (100%)
ß blockers	30 (100%)	29 (97%)
Statins	28 (93%)	28 (93%)

BMC=bone-marrow cell. ACE=angiotensin-converting enzyme. Data are means (SD) or n (%) unless otherwise stated. *Serum cholesterol >5·2 mmol/L. †Patients not receiving aspirin were treated with phenprocoumon.

***Table 1:* Patients' characteristics**

Mean time from PCI to baseline cardiac MRI was 3·5 days (SD 1·5). Mean time from PCI to bone-marrow harvest was 4·8 days (1·3). Time from symptom onset to harvest of bone-marrow cells was 5·7 days (1·2). On average, 128 mL (33) of bone marrow was aspirated from the posterior iliac crest during a brief general anaesthesia with midazolam and etomidate. No bleeding complications at the harvest site were noted.

During preparation of bone-marrow cells, the sedimentation process reduced the volume of bone-marrow cells to a mean of 26 mL (SD 4) and recovered 75% (12) of nucleated cells from the initial bone-marrow aspirate. The final preparation of bone-marrow cells contained $24{\cdot}6\times10^8$ (SD $9{\cdot}4\times10^8$) nucleated cells (viability 99% [2]), $9{\cdot}5\times10^6$ ($6{\cdot}3\times10^6$) CD34+ cells, and $3{\cdot}6*10^6$ ($3{\cdot}4\times10^6$) haemopoietic colony-forming cells. The packed cell volume of the final bone-marrow-cell preparation was 31% (11), and the platelet count was 182×10^6 (93×10^6) per mL .

Changes of LVEDV index, LVESV index, left-ventricular-mass index, and late-contrast enhancement from baseline to 6 months' follow-up did not differ significantly between the control and bone-marrow-cell groups (table 2). The increase in LVEDV index at 6 months was slightly higher in the bone-marrow-cell group, whereas LVESV index tended to decrease more in the bone-marrow-cell group (table 2). 6 months after randomisation, global LVEF increased significantly in the bone-marrow-cell group compared with controls (p=0·0026) (table 2 and figure 2). The effects of bone-marrow-cell transfer on global LVEF change at 6 months' follow-up were consistent in all investigated subgroups (figure 3). The improvement in global LVEF after 6 months' follow-up was not correlated with the number of nucleated cells (r= -0·11, p=0·57), CD34+ cells (r=0·13, p=0·48), or haemopoietic colony-forming cells (r= -0·14, p=0·46) infused into the infarct-related coronary artery.

	Baseline		**6 months**		**Change**		**BMC treatment effect***	**p**
	Controls	BMC group	Controls	BMC group	Controls	BMC group		
LVEDV index (mL/m^2)	81·4 (16·9)	84·2 (17·2)	84·9 (21·9)	91·7 (26·0)	3·4 (11·1)	7·6 (20·0)	4·0 (-4·4 to 12·5)	0·32
LVESV index	40·6 (16·9)	43·0 (14·7)	42·6 (23·5)	42·4 (23·9)	2·0 (11·1)	-0·6 (14·9)	-3·2 (-9·7 to 3·3)	0·33

(mL/m^2)									
Global LVEF (%)	51·3 (9·3)	50·0 (10·0)	52·0 (12·4)	56·7 (12·5)	0·7 (8·1)	6·7 (6·5)	6·0 (2·2 to 9·9)	0·0026	
LVM index (g/m^2)	78·2 (18·3)	82·7 (18·7)	71·7 (14·2)	71·9 (14·6)	-6·5 (12·8)	-10·8 (10·6)	-2·5 (-7·3 to 2·3)	0·30	
LE (mL)	30·3 (17·4)	33·0 (21·1)	19·8 (9·8)	18·9 (12·2)	-10·5 (10·6)	-14·1 (13·0)	-2·2 (-5·4 to 1·0)	0·18	

BMC=bone-marrow cell. Data are mean (SD) unless otherwise stated. *Treatment effects expressed as differences in least-squares means (ANCOVA model) with 95% CI. LVM=left ventricular mass. LE=late contrast enhancement. There were no differences between groups at baseline.

Table 2: **Left ventricular volume and mass indices, global LVEF, and late enhancement as determined by contrast-enhanced MRI at baseline and 6 months' follow-up**

Figure2: **Global LVEF at baseline and 6months' follow-up**

*p=0·0026 for difference between groups. Small dots show data for individual patients; large dots show mean values. Vertical bars show SD.

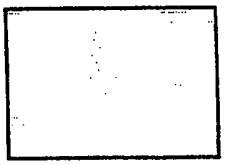

Figure3: **Subgroup analyses of global LVEF changes from baseline at 6months' follow-up**

LE=late contrast enhancement. BMC=bone-marrow cell. *Median values of the whole study population were used to create subgroups of equal size. ŶCardiovascular risk factors were diabetes, total cholesterol concentration greater than 5·2 mmol/L , hypertension, or current smoking. Oval dots show differences of least-squares means between groups; horizontal bars show 95% CI.

Compared with the control group, patients in the bone-marrow-cell group had increased regional LVEF (p=0·04) and systolic wall motion in the border zone (p=0·03) at 6 months. By contrast, systolic wall motion in the infarct region was not significantly enhanced by transfer of bone-marrow-cells (table 3). Representative colour-coded images showing the effects of bone-marrow-cell transfer on left-ventricular function are shown in figure 4.

	Baseline		**6 months**		**Change**		**BMC treatment effect†**	**p**
	Controls	BMC group	Controls	BMC group	Controls	BMC group		
Regional LVEF	47·8 (9·7)	46·3 (10·6)	48·9 (15·2)	53·0 (15·5)	1·1 (11·8)	6·7 (9·5)	5·7 (0·2 to 11·3)	0·04

(%)							
Systolic wall motion (mm), infarct region	3·9 (1·8)	4·4 (1·9)	4·9 (2·9)	5·9 (2·5)	1·0 (2·5)	1·5 (2·1)	0·6 (-0·6 to 1·8)	0·32
Systolic wall motion (mm), border zone	6·8 (1·6)	7·0 (1·7)	6·8 (2·1)	8·0 (2·1)	-0·1 (2·2)	1·0 (1·9)	1·1 (0·1 to 2·1)	0·03

BMC=bone-marrow cell. Data are mean (SD). Treatment effects are expressed as differences in least-squares means (ANCOVA model) and 95% CI· There were no differences between groups at baseline·

Table 3: **Regional LVEF and systolic wall motion as determined by contrast-enhanced MRI at baseline and 6 months' follow-up**

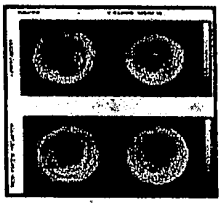

Figure4: **Representative colour-coded images showing systolic wall motion at baseline and 6months' follow-up in two patients**

Both patients had had an anterior acute myocardial infarction. Bright colours indicate good systolic wall motion, whereas dark colours indicate poor wall motion (expressed in mm). Note improved functional recovery in the patient treated with bone-marrow-cells.

No patient died or was lost to follow-up. There were no increases in troponin T concentrations in serum in any of the patients 24 h after intracoronary transfer of bone-marrow cells, indicating that the procedure did not inflict additional ischaemic damage to the myocardium. In 6 months of follow-up, three controls and one patient from the bone-marrow-cell group needed at least one hospital admission for worsening heart failure. One person from the bone-marrow-cell group developed a non ST-segment elevation myocardial infarction in the left circumflex territory 4 months after transfer of bone-marrow-cells into the left anterior descending coronary artery. This patient underwent PCI of the left circumflex coronary artery and completed the study.

There were no differences between the control and bone-marrow-cell groups with respect to the number of premature ventricular complexes per h and the occurrence of non-sustained or sustained ventricular tachycardias by Holter monitoring at 6 weeks', 3 months', and 6 months' follow-up. 28 (93%) controls and 27 (90%) patients who had bone-marrow-cell transfer agreed to undergo an electrophysiological study at 6 months' follow-up. A non-sustained ventricular tachycardia was inducible in one control patient and in one bone-marrow-cell transfer patient. Ventricular fibrillation was inducible in one control patient. In 29 (97%) controls and 28 (93%) patients who had bone-marrow-cell transfer, coronary angiograms were obtained at 6 months' follow-up. Mean in-stent restenosis in the infarct-related artery, expressed as a percentage of luminal diameter, was 32% (SD 20) in the control group and 33% (23) in the bone-marrow-cell group (p=0·88). Four

patients from the control group and seven from the bone-marrow-cell group presented with an in-stent restenosis of at least 50% (p=0·28). One patient from the control group developed total in-stent occlusion.

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Discussion

Our randomised controlled clinical trial addresses the effect of autologous bone-marrow-cell therapy on left-ventricular functional recovery after acute ST-segment elevation myocardial infarction. We have shown that infusion of autologous bone-marrow-cells into the infarct-related coronary artery during the early postinfarction period (4-8 days after symptom onset) improves recovery of global LVEF after 6 months.

In view of the size of our trial, subgroup analyses must be considered with caution. With this caveat in mind, it is noteworthy that the effects of bone-marrow-cell transfer on global LVEF change were consistent across all investigated subgroups. The effects of cell transfer were over and above benefits associated with established strategies to promote functional recovery after acute myocardial infarction, such as PCI with stent implantation, and postinfarction pharmacotherapy with ACE-inhibitors, angiotensin-receptor blockers and ßblockers.[11,12]

Global LVEF at baseline was 51% (SD 10) in our patient cohort, which is consistent with previous MRI studies in patients after myocardial infarction.[14,15] In healthy adults, normal LVEF values of 67% (5) have been shown with MRI.[16] Therefore, patients enrolled in our study had substantial functional impairment. Global LVEF increased by only 0·7 percentage points after 6 months' in the control group, emphasising the need for additional therapeutic strategies to enhance functional recovery in patients with acute myocardial infarction. Since 40% of patients had been transferred for rescue PCI from outside hospitals, the average time from symptom onset to PCI was quite long in our trial (median 8·5 h). Previous studies have shown that greater LVEF improvement (up to 4 percentage points) can be achieved when coronary patency is re-established within 4 h of symptom onset.[17,18] Of note, however, is that in these studies baseline LVEF was measured within 24 h of PCI.[17,18] By contrast, we assessed baseline LVEF 3·5 days (SD 1·5) after PCI, at a time when left-ventricular function is likely to have partly recovered from postischaemic myocardial dysfunction (ie, stunning).[19] Similar to the results obtained in our control group, two MRI studies that used serial LVEF measurements in patients with reperfused myocardium after acute myocardial infarction have reported no significant improvement in LVEF from a baseline investigation at day 5-7, to follow-up at 3-6 months.[14,15]

Improvement of global LVEF in the treatment group was due mostly to improved regional systolic wall motion in the infarct border zone. Left-ventricular end-diastolic volumes did not decrease, indicating that transfer of bone-marrow-cells did not improve left-ventricular remodelling at 6 months. Longer follow-up of our patients is required (and will be done) to assess the impact of bone-marrow-cell transfer on long-term left-ventricular structural adaptation after acute myocardial infarction.

Because of ethical considerations, we decided not to do bone-marrow aspiration and a sham left-heart catheterisation in patients randomised to the control group. Importantly, however, all MRI data were analysed by two investigators who were not aware of treatment assignments.

Our study was not designed to assess underlying mechanisms of treatment with bone-marrow-cells that promote functional recovery after acute myocardial infarction. Apparently, transdifferentiation of bone-marrow-derived haemopoietic stem cells to cardiomyocytes cannot account for the beneficial effects.[20,21] Instead, recent papers have highlighted the potential of bone-marrow cells to promote paracrine effects in ischaemic tissues (eg, secretion of angiogenic factors), and suggest that paracrine signalling, rather than cell incorporation, promotes functional recovery.[5,22-25]

Our experience suggests that intracoronary bone-marrow-cell transfer is safe; specifically, there was no evidence for an increased rate of in-stent restenosis or proarrhythmic effects. It should be noted that high rates of in-stent restenosis have been reported after intracoronary transfer of granulocyte colony-stimulating-factor mobilised peripheral-blood mononuclear cells.[26] Importantly, granulocyte colony-stimulating factor, which may promote in-stent restenosis by enhancing neutrophil recruitment at sites of tissue injury,[27] was not used in our study. Intracoronary injection of bone marrow-derived mesenchymal stromal cells has been shown to cause microinfarctions in dogs.[28] It should be noted that nucleated bone-marrow cells are significantly smaller than expanded mesenchymal stromal cells ex vivo,[28] which may explain why we, and others,[10] did not observe infarctions (ie, increases in concentrations of troponin T in serum) after intracoronary transfer of bone-marrow cells.

Our results lend support to the concept that autologous bone-marrow cells can be used to enhance left-ventricular functional recovery in patients after acute myocardial infarction. Larger trials are needed to address the effect of bone-marrow cell transfer on clinical endpoints such as the incidence of heart failure and survival.

Contributors

K C Wollert contributed to study design, enrolment, and clinical follow-up of patients, aspiration and intracoronary transfer of bone marrow, and the writing of the manuscript. G P Meyer contributed to study design, enrolment of patients, MRI data acquisition, and intracoronary BMC transfer. J Lotz contributed to MRI data acquisition. C Breidenbach and S Fichtner analysed MRI data. S Ringes-Lichtenberg contributed to enrolment and clinical follow-up of patients. T Korte did electrophysiological studies. B Hornig did intracoronary transfer of bone-marrow cells. P Lippolt and D Messinger did statistical analyses. L Arseniev did bone-marrow-cell sedimentations. B Hertenstein and A Ganser contributed to study design and did bone-marrow aspirations. H Drexler contributed to study design and the writing of the manuscript.

Conflict of interest statement

L Arseniev is business unit leader of Cytonet Hannover, the company that did the bone-marrow-cell sedimentations during the trial. L Arseniev has not been involved in any way in MRI data collection or data analysis in this trial.

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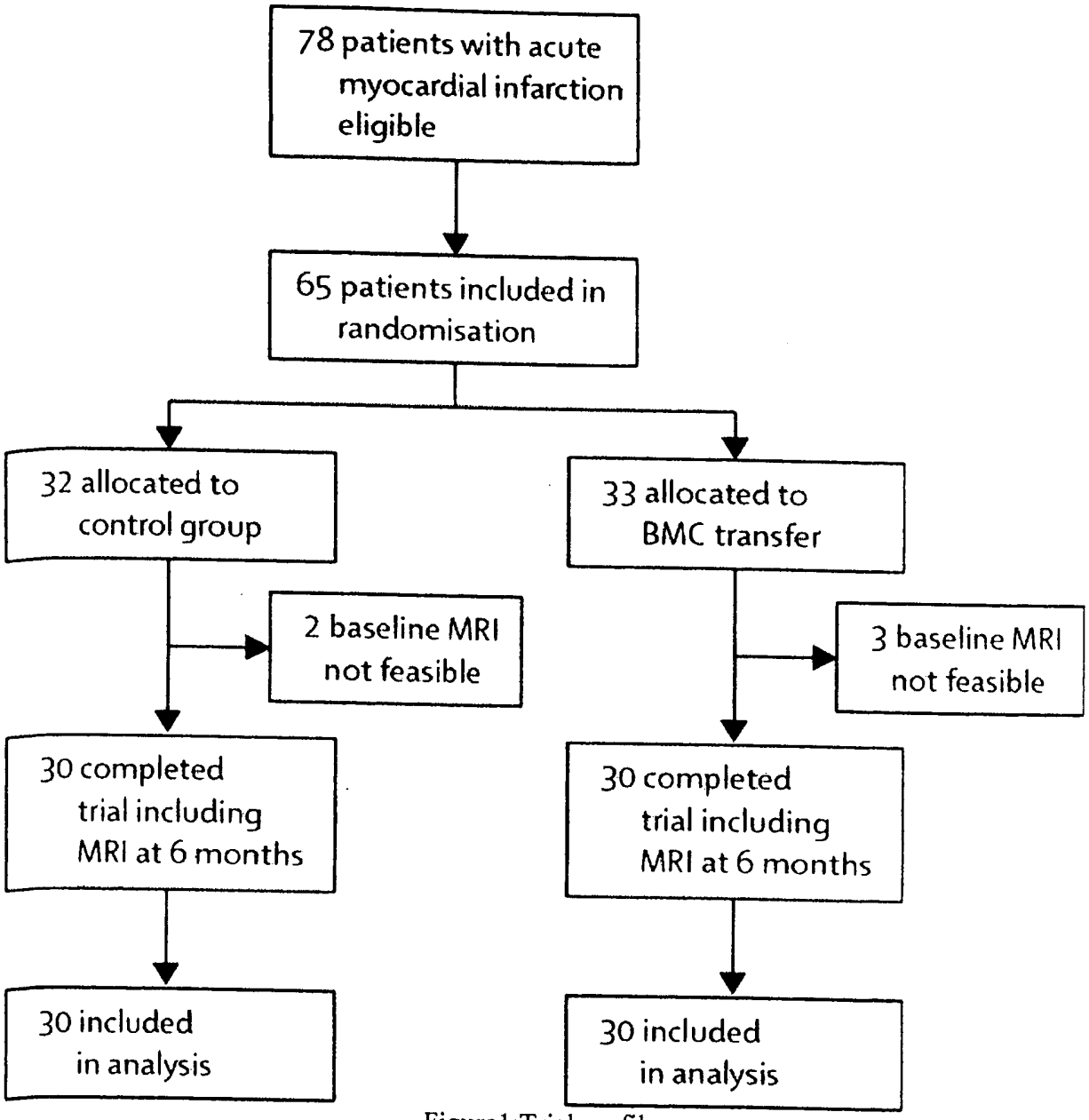

Figure1:Trial profile

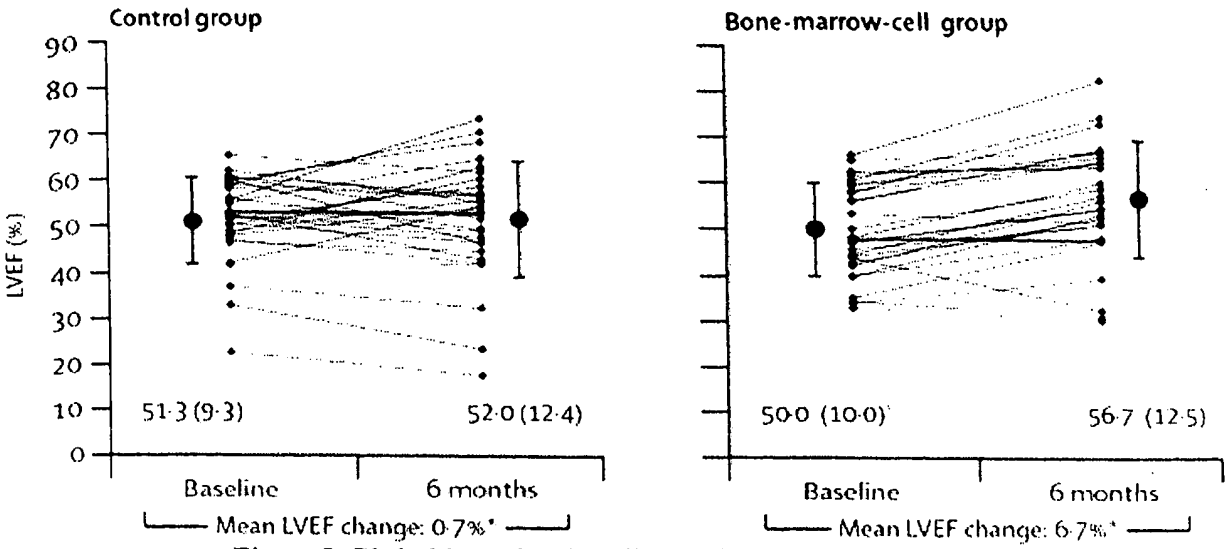

Figure2:Global LVEF at baseline and 6months' follow-up

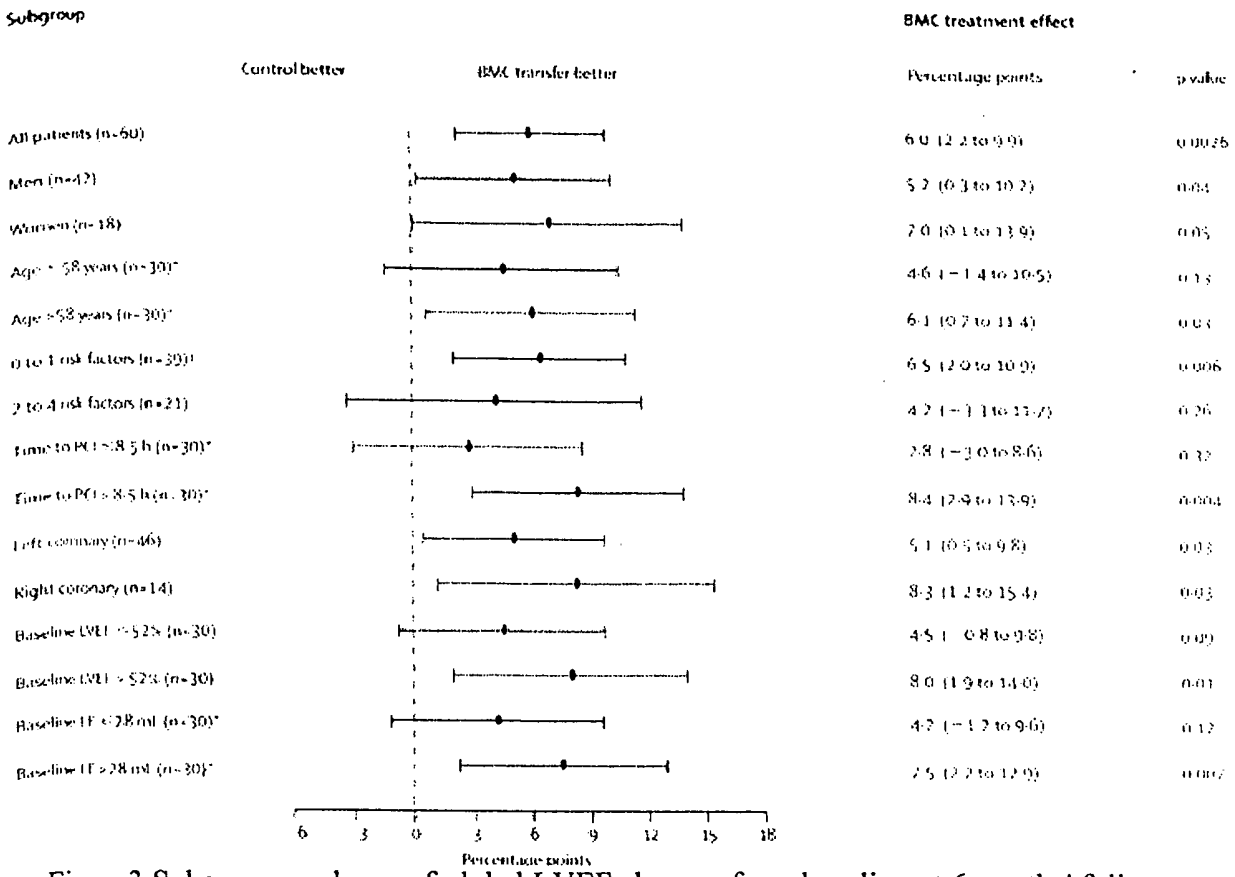

Figure3:Subgroup analyses of global LVEF changes from baseline at 6months' follow-up

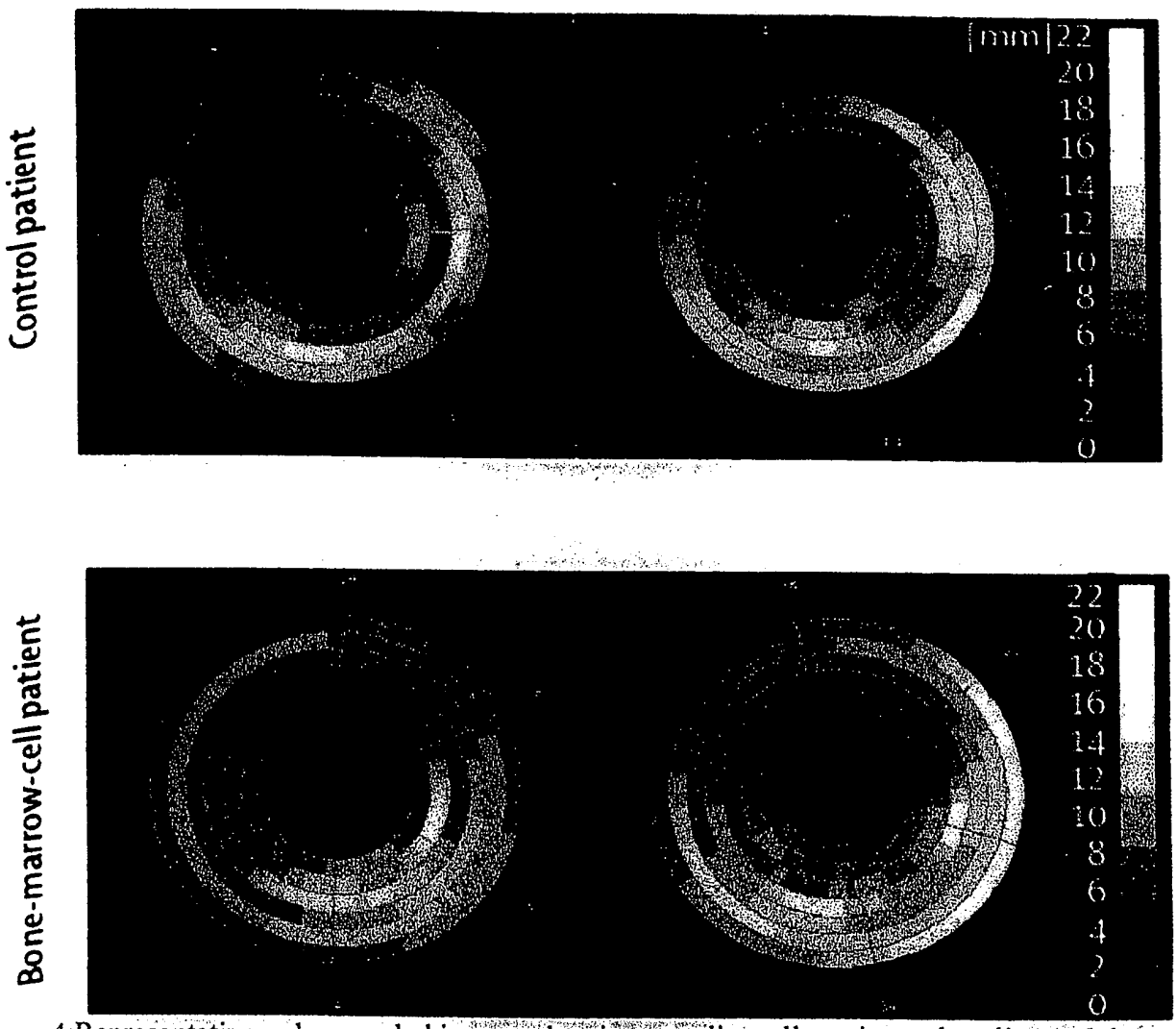

Figure4:Representative colour-coded images showing systolic wall motion at baseline and 6months' follow-up in two patients

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